WHY WE NEED LEGAL STANDARDS FOR PEDIATRIC RESEARCH

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Pediatric research is needed to improve pediatric medicine and ensure the safety and efficacy of the approximately 70% of current medications that lack sufficient data in children.[1-3] Yet pediatric research raises difficult ethical issues, and there is continuing debate regarding its appropriateness.[4-6] Although ethical debate over aspects of pediatric research is perhaps inevitable and likely healthy, improving pediatric medicine requires standards for when investigators may conduct pediatric research without the potential for legal liability.

Commentators have assumed that federal regulations protect investigators from being sued successfully.[7,8] However, the federal regulations only establish guidelines for how pediatric research must be conducted to receive federal funding or product approval by the Food and Drug Administration. These regulations do not specify when it is lawful to conduct pediatric research, leaving the parties involved in pediatric research—institutions, investigators, parents, and children—without legal guidance and vulnerable to liability in state court.

In the absence of legal standards, the Maryland Court of Appeals regarded the case of *Grimes v. Kennedy Krieger Institute* (KKI) as an opportunity to "write on a clean slate" regarding whether investigators who conduct research in compliance with the federal regulations can be held liable in state court.[9] After the court's ruling, the Maryland legislature adopted a statute governing human subjects research.[10] Without a uniform alternative, legislatures in some states and courts in others are likely to follow suit, yielding a patchwork of laws across the country. To ensure the viability of efforts to improve pediatric medicine through research and protect the parties involved in these efforts, it is vital to develop uniform laws governing pediatric research.

GRIMES CASE

The *Grimes* case stems from a KKI-sponsored study conducted in Baltimore, Maryland, from 1993 to 1995, designed to identify an economical method of partial lead paint abatement that protects children from lead poisoning. Parents of two children enrolled in the study sued KKI, alleging investigators failed to warn them in a timely manner when elevated levels of lead dust were found in the plaintiffs' homes. KKI responded that the investigators' research relationship with subjects did not give rise to a duty to warn of potential dangers found using unproven methods. The lower court agreed and dismissed the case. The plaintiffs appealed to the Court of Appeals, Maryland's highest court.

The Maryland Court of Appeals recognized that existing federal regulations for pediatric research are tied to provision of federal funds.[7] To receive federal funds, institutions conducting human subjects research, including pediatric research, must agree to abide by the federal regulations.[7] Institutions that so agree and then fail to follow the federal regulations are subject to administrative sanctions. Yet there are no standards for what types of pediatric research protect investigators from legal liability. For instance, there are no legal standards implying that investigators who conduct research in accordance with federal regulations are protected from liability under state law. Instead, individual courts will decide at the time particular cases are brought before them whether adherence to federal regulations is sufficient to protect institutions, investigators, and even parents from legal liability.

In the *Grimes* case, the Maryland Court of Appeals found that adherence to federal regulations is not sufficient, ruling that an entire category of pediatric research—minor increase over minimal risk, no prospect of direct benefit research—allowed under federal regulation nonetheless places investigators and institutions at risk of legal liability.[11-13]

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IRB	Institutional Review Board	KKI	Kennedy Krieger Institute

Since the court's ruling, the Maryland legislature has passed a statute allowing this category of research.[10] To ensure the continued viability of pediatric research, it is vital to establish laws that allow investigators, institutions, and parents to determine prospectively which types of pediatric research place them at risk for legal liability.

LEGISLATION RATHER THAN LITIGATION

Laws governing pediatric research could be developed simply by waiting for state courts to produce comprehensive and, ideally, consistent guidance. Unfortunately, the nature of judicial adjudication suggests that this approach may not yield appropriate standards. First, courts base their rulings on the specific facts of individual cases. Hence, standards developed by individual courts may not be generalizable, and courts that hear different cases may endorse different standards. Second, although judges and juries issue the final decisions, they typically do not control presentation of the facts, and the adversarial legal system does not encourage lawyers to provide judges with a complete and unbiased account of relevant facts. Third, reliance on the courts entails that development of comprehensive laws must await a sufficient number of cases that raise the relevant issues. The resulting delay before it is clear when pediatric research is lawful could have a chilling effect on attempts to improve pediatric medical care.

Passage of legislation offers one way to address these concerns. Legislators, unlike judges, are not restricted to the facts of the cases brought before them, can solicit testimony from the public and individual experts, and can develop standards proactively, thus avoiding a long delay in developing legal standards for pediatric research. A few state legislatures have passed statutes that incorporate the federal regulations.[10,14] Several others have laws that mention federal regulations for insurance coverage, private health information, or informed consent.[15] Similarly, several laws and legal precedents indirectly relate to pediatric research. For instance, the *Grimes* court cited legal precedents that parents' decisions should be in children's best interests. Finally, many states have consent laws for children's medical treatment, although their implications for research, especially nonbeneficial research, are unclear.[16]

The continued adoption of different standards by state legislatures could block ethically appropriate, multistate research, allow investigators to shop protocols to states with the most favorable laws, and fail to provide children appropriate protection. Federal legislation, such as two bills proposed in the previous session of the US Congress to expand federal regulations to protect human subjects, could yield legal standards that address these concerns.[17,18]

Legislators, although not bound by restrictions on courts, may not have the time or expertise necessary for an in-depth assessment of the appropriate ethical standards on which to base laws governing pediatric research. An alternative would be to appoint an independent, diverse, and widely respected group of experts and laypersons to develop a model statute for Congress or individual states to adopt. Model statutes are particularly effective in areas of medicine and science that raise complex ethical issues of widespread social import, as illustrated by the Uniform Determination of Death Act and the Uniform Anatomical Gift Act.[19,20]

DEVELOPING LAWS GOVERNING PEDIATRIC RESEARCH

To ensure consistency, legal standards for pediatric research should be developed in concert with legal standards for all human subjects research. The development of laws for human subjects research in general could be guided by the numerous recent systematic assessments of the ethics of human subjects research.[21-24] In contrast, pediatric research has not received comprehensive assessment in the past 30 years. This suggests that legal standards governing pediatric research should not simply adopt current federal regulations. Instead, development of legal standards should be regarded as an opportunity to review the ethical issues raised by pediatric research and assess the extent to which current federal regulations address them. In this regard, four aspects of pediatric research deserve particular attention: (1) risk and benefit, (2) subject selection and recruitment, (3) consent and assent, and (4) approval and monitoring.

Risk and Benefit

Some pediatric research offers a compensating potential for direct benefit. For instance, the potential medical benefits of phase III drug trials often outweigh the risks. Current acceptance of potentially beneficial research has concealed a lack of clarity over *which* benefits justify the risks of pediatric research. This issue was highlighted by an Office for Human Research Protections ruling that psychological benefits from donating bone marrow to a sick sibling can justify the risks of pediatric research. Do psychological or altruistic benefits justify research risks only when the recipient is a first-degree relative? Can other potential benefits, such as research scans that may reveal undetected tumors, justify research risks as well?

Pediatric research that does not offer a compensating potential for direct benefit has generated substantial controversy.[25-28] The federal regulations allow children to be enrolled in nonbeneficial research that poses "minimal" risk, defined as the risks of "daily life," and nonbeneficial research that poses a "minor increase over minimal" risk.[7] Criticism of the federal definition of minimal risk has focused on its lack of clarity, largely ignoring the fact that it has a fundamental flaw. The risks children face in everyday life—for instance, the risks posed by school field trips—often are justified by the potential for personal benefit. Hence, these risks do not seem to provide an appropriate standard for the risks to which children may be exposed in the context of nonbeneficial research. Experts who develop legal standards for pediatric research should consider whether a new risk standard, based on the risks to which children may be exposed for the benefit of others, is needed for nonbeneficial pediatric research.

Subject Selection and Recruitment

There is widespread agreement that children should be enrolled in nonbeneficial research only when their participation is necessary to answer the question posed. Federal regulations attempt to ensure that this safeguard is met by allowing children to be enrolled in nonbeneficial research that poses a minor increase over minimal risk only when it is likely to yield "generalizable knowledge about the subject's disorder or condition."[7] Unfortunately, this "subject's condition" requirement allows investigators to enroll children in such research, even when their participation is not necessary. For instance, the federal regulations allow children with epilepsy to be enrolled in nonbeneficial research on epilepsy when the scientific question could be answered by enrolling only adults who have epilepsy. This possibility suggests that legal standards for pediatric research should replace the current subject's condition requirement with an explicit requirement that children may be enrolled in nonbeneficial research only when the scientific question cannot be answered by enrolling only adults who can consent.

Consent and Assent

With few exceptions, federal regulations require investigators to obtain parental permission and the assent of children who are capable of providing it.[7,8] However, federal regulations do not specify which children are capable of assent, or even what abilities a child must have to be capable of providing assent. This lack of guidance has led to widespread variation in Institutional Review Board (IRB) practice, with approximately half of all IRBs having no method for determining which children are capable of assent, and the remainder using a variety of age cutoffs, ranging from younger than age 5 years to older than age 10 years (unpublished data).

To determine the appropriate age cutoff, it will be necessary to determine which capacities children must possess to give assent and, based on the most recent data on child development, when most children develop these capacities. In addition, experts who develop laws for pediatric research should consider adopting an explicit requirement that investigators must respect children's sustained dissent.

Approval and Monitoring

The fact that pediatric research involves subjects who cannot consent raises the question of whether the standard review and approval process is sufficient for pediatric research. Most importantly, it may make sense to require IRBs to provide ongoing monitoring of pediatric research. Similarly, it will be important to assess whether the approval of pediatric research, especially nonbeneficial research, should require a super majority, rather than the simple majority of IRB members required under current federal regulation.

Next, federal regulations allow the Secretary of the Department of Health and Human Services or the Commissioner of Food and Drugs to approve research that is "not otherwise approvable" under the regulations.[7,8] It may be important to assess on what grounds research may be approved by other parties when it cannot be approved by the reviewing IRB. Finally, it seems appropriate to incorporate a mechanism for periodic review to ensure any laws continue to provide appropriate protection as thinking evolves and new issues emerge.

CONCLUSION

The federal regulations do not protect the parties involved in pediatric research from legal liability. Recent events in Maryland highlight that individual courts and state legislatures may attempt to address this situation by developing their own laws governing pediatric research. The resulting patchwork of laws may block appropriate pediatric research, place investigators, parents, and institutions in legal jeopardy, and fail to protect children adequately. We have argued that these concerns could be addressed by development of uniform laws governing pediatric research in concert with development of laws for human subjects research in general.

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